EVALUATION OF C-REACTIVE PROTEIN AS EARLY INDICATOR OF BLOOD CULTURE POSITIVITY IN NEONATES

Mustafa S[1], Farooqui S[2], Waheed S[3] & Mahmood K[4]

ABSTRACT

Objective: To determine the Sensitivity, Specificity and Predict values of C - reactive protein as an early indicator of Neonatal Sepsis.

Design: It was an observational study of newborns suspected sepsis.

Place & Duration of study: The study was carried out in the Department of Paediatrics, Karachi Medical & Dental College and Abbasi Shaheed Hospital, Karachi over a period of eight months (March 1, 2001 to October 31,2001).

Patient & Methods: Neonates admitted to intensive care nursery of the Abbasi Shaheed Hospital Karachi were evaluated for Neonatal Sepsis. C-reactive protein as screening test was performed along with blood culture from peripheral venepuncture. The gold standard for the Diagnosis of Sepsis was positive blood culture.

Result: The positive C- reactive protein found in 14 of 21 episodes associated with the positive blood culture, but in 15 of 29 negative cases it was also found positive. The sensitivity and specificity are equal to negative predict value and positive predict value respectively i.e. 66.66% and 48.27%.

Conclusion: CRP estimation have some value in early diagnosis of Neonatal sepsis but the frequent occurrence of raised CRP in sera of uninfected neonates eliminates it as a useful indicator of infection but may suggest an active tissue damaging process. We do not advocate to rely on the result of single test, even with the combination of test, we still stress the importance of correlating the clinical and laboratory data. We recommend that a scoring system should be designed for our setup, using those test that are easy to perform, economical, reliable, should have high predictive value and should ideally identify all infected infants (high sensitivity).

KEY WORDS: C - reactive protein, Neonatal Sepsis, Acute phase response.

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1. Dr. Sultan Mustafa
Assistant Professor & Incharge
Department of Paediatrics
2. Dr. Shamsa Farooqui
Senior Registrar of Paediatrics
Dept. of Paediatrics
3. Dr. Sumbal Waheed
Registrar: Dept. of Pathology
4. Dr. Kamal Mahmood DCH,
Dept. of Pediatrics

1-4. Karachi Medical & Dental College
and Abbasi Shaheed Hospital,
City District Government, Karachi, Pakistan

Correspondence:
Dr. Sultan Mustafa
B - 9, Block 17, F.B. Area, Karachi, Pakistan
E-mail: Peadash@hotmail.com

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INTRODUCTION

Sepsis in neonates may be difficult to differentiate from other conditions because the clinical signs are non- specific.[1] It is a common cause of morbidity and mortality amongst the neonates in intensive care units. Delay of even few hours in initiating treatment can increase the morbidity and mortality considerably. Traditional methods such as blood culture do not provide a rapid diagnosis. However tests are available which can identify neonates who do have bacterial infection.[2] It has been suggested that a combination of hematological and biochemical test may provide a more rapid and accurate diagnosis of bacteremia than conventional microbiological methods.[3]

The concentration of many serum proteins rise in response to inflammation associated with infection,trauma or tissue damage. This is called acute phase protein or acute phase response. Among these proteins the important being C-reactive protein,haptoglobin and fibrinogen. These can be used as a non-specific indicator of bacterial sepsis.

In this study the role of C-reactive protein as early indicator of Neonatal sepsis was evaluated. Selected test is the reflection of acute phase response of inflammations in neonates which could be performed rapidly and economically.

PATIENTS AND METHODS

Newborns admitted to the intensive care nursery of the Abbasi Shaheed Hospital Karachi were evaluated for neonatal sepsis. The unit admits about 500 babies each year with both medical and surgical illnesses. Infants were evaluated for neonatal sepsis if risk factors or clinical manifestations of sepsis were present (table I). The principal risk factors were Prematurity (<36 weeks), low birth weight (<2.5Kg), evidence of perinatal maternal infection, prolonged rupture of membranes (>24 hours,) birth asphyxia, home delivery and instrumentation. The principal clinical factors were reluctant to feed, poor reflexes (sucking, moro), temperature instability, respiratory distress, irritability, abdominal distention and unexplained apnea or cyanotic spell.

Neonates admitted between 1st March 2001 to October 31st, 2001 were evaluated, if there were predisposing risk factors or a clinical suspicion of sepsis (table-I). Fifty (50) evaluation for sepsis were performed during this period. Each neonate was examined by a registrar who recorded on a data acquisition sheet predisposing prenatal factors, clinical features, and a subjective clinical impression as to the presence or absence of sepsis before investigation were instituted (table I &II). Those who received prior antibiotic before admission were excluded from study. C-reactive protein as screening test was performed along with blood culture from peripheral venipuncture.Urine culture and C.S.F culture were done when indicated. The diagnosis of sepsis was made when there were positive findings on cultures. Neonates with negative blood cultures may have sepsis but this study was designed to assess the role of CRP in culture positive cases.

C-reactive protein was checked by latex method. The latex test is slide agglutination test with addition of a drop of reagent (antisera) to a drop of serum with gentle agitation for four to five minutes, which can easily be performed at the bedside or under laboratory supervision.

Sensitivity, Specificity, Positive predict value and Negative predict value were calculated in both culture positive and culture negative cases.

RESULTS

Prevalence of sepsis

Sepsis was confirmed (positive blood culture) in 42%(21of 50) of evaluation. Ten out of 29 culture negative cases were identified as sepsis on clinical impression, excluding other illnesses and response to antibiotic therapy. Fourteen of twenty-one culture positive cases (66.66%) were 2 or <2 days while 33.33% (7 of 21) were >2 days. Mean age of onset was 4 days (range 12 hr to 20 days).

Birth weight and gestational age

Sixty six percent (33 of 50) were 2.5 or <2.5-Kg. The mean weight was 2.32Kg (range 1.3-4.12 Kg). 22 out of 50 were born before term (<36 weeks). The mean gestational age was 35.5 wks (range 31.5-39.5wks).

Risk factors

Major risk factors associated with development of sepsis (table-II) were low birth weight (50%), prematurity (36%) birth asphyxia ((34%), prolonged rupture of membrane >24 hrs(30%), instrumental delivery(24%), caesarean section(16%), major clinical presentation were temperature instability (fever or hypothermia) 76%, reluctant to feed 54%, respiratory

distress 40%, jaundice 20%, abdominal symptoms (distention, vomiting, diarrhea) 18%, CNS sign 16%, hepatomegaly 12%.

Performance of Screening test

The positive C-reactive protein found in 14(66.66%) of 21 neonates who had positive blood culture and in 15 of 29 (51.72%) neonates with negative blood culture. Total number of Sepsis identified 31 (21 culture +ve & 10 culture –ve). C-reactive proteins were found positive in 14 culture positive cases and 10 out of 29 culture negative cases. Sensitivity, specificity, negative predict value & positive predict value of CRP in culture negative cases were 60%, 78.94%, 31.57% and 60% respectively.

The overall sensitivity and specificity of all culture positive and culture negative cases are equal to negative predictive value and positive predictive value respectively i.e. 66.66% and 48.27%.

Clinical diagnosis and evaluations:

Neonatal Sepsis 31 (21 culture positive & 10 culture negative were diagnosed on clinical risk factors and response of antibiotic therapy). Ten children had birth asphyxia, hypoglyce-

Table-I: Environmental & clinical risk factors of neonatal sepsis

Perinatal risk factors
- Prematurity
- Low birth weight
- Prolong rupture of membrane (>24 hrs.)
- Perinatal maternal infection
- Birth asphyxia
- Operative delivery
- Twining
- Assisted ventilation
- Instrumentation

Environmental risk factors
- Low socioeconomic status
- Home delivery
- Parental nutrition
- Surgical procedure
- Central venous line
- Contaminated equipments
- Obstetric procedure (eg external or internal version)
- Frequent vaginal examination

Host risk factors
- Male sex
- Omphalitis
- Galactosemia
- Congenital anomaly (e.g. asplenia,meningomyelocele)
- Immune defect

Clinical risk factors

General
- Fever/ hypothermia
- Reluctant to feed

CNS features
- Irritability,lethagy
- Convulsions
- Abnormal moro reflex
- Full fontanel
- Hi pitched cry
- Hyporeflexia / hypotonia

Hepatobiliary feature
- Abdominal distention
- Vomiting
- Diarrhea
- Hepatomegaly
- Splenomegaly
- Jaundice

Respiratory feature
- Apnea / dyspnea
- Tachypnea / retraction
- Flaring / grunting
- Cyanosis

Skin
- Sclerema
- Pallor,mottling,cold clammy skin
- Petechiae,purpura

Source: Nelson Textbook of Pediatrics, 15th. Edition, pp. No. 517.

Table-II: Risk factors for neonatal infection identified during evaluations

Perinatal risk factors %(numbers)	*Clinical risk factors %(numbers)*
• Low birth weight 50(25) • Prematurity36(18) • Birth Asphyxia 34(17) • Home delivery 32(16) • PROM>24hrs.30(15) • Instrumentation 24(12) • Caesarean section 16(8) • Omphalitis 6(3) • Perinatal maternal infection 4(2) (maternal fever)	• Fever or hypothermia 76(38) • Reluctant to feed 54(27) • Respiratory distress 40(20) • Jaundice 20(10) • Abdominal feature 18(9) • CNS feature 16(8) • Hepatomegaly 12(6) • Splenomegaly 12(6) • Petehiae / purpura 10(5) • Pallor,mottling, cold clammy skin 10(5) • Sclerema 8(4)

PROM-Prolong rupture of membrane

mia was seen in five while three were suffering from respiratory distress syndrome.

Result of CRP in Culture Negatives Neonates (29 of 50) showed CRP positive in six infected neonates and four non-infected neonates. CRP was negative in four infected and fifteen non-infected neonates. Ten out of 29 culture negative cases were identified as infected on clinical ground, excluding other illness and response to antibiotic therapy.

Performance of CRP in culture negative cases showed a sensitivity of 60%, specificity of 78.94%. It had negative predict value in 31.57% and positive predict value in 60%.

DISCUSSION

The diagnosis of sepsis requires microbiological and clinical correlation. Twenty-nine (29) infants classified as having probable infection had clinical evidence but they lacked microbiological proof of infection. This was probably because of administration of intrapartum antibiotic, which influenced the culture results. Statistical analysis would be simplified if latter infants were excluded from the study, but we cannot ignore these infants because fatal infection has been reported in the presence of negative blood culture.[4] Second problem in dealing with sepsis is delay in diagnosis. Blood culture will take at least 24-48 hours but delay of even few hours in initiating treatment will increase the morbidity and mortality considerably.

None of the tests gave the sensitivity, specificity and positive predictive accuracy of the combined results of acridine orange leucocyte cytospin (AOLC), nitroblue tetrazolium (NBT) and C-reactive protein (CRP),[5] but the former two tests are not available in our setup although NBT is available at AKUH but takes more time than result obtained from culture report. So the test was selected on the basis of ease, speed of performance, cost and availability. This test has practical advantages: it is applicable to all infants including those who have received Antibiotic therapy prior to evaluation,[6] it should save time for the busy physician particularly the inexperienced house officer; and it could allow a more systemic approach to decision regarding antibiotic therapy. However, we would still stress the importance of correlating both clinical and laboratory data, because few infants in our study proved to have sepsis on the first day of life but had no symptoms at the time of evaluation and were included in the study because of intrapartum risk factors. Similarly the infants who would otherwise have been missed by these had clinical features of sepsis.

Raised serum level of CRP are found in 50-90% neonates from six hours of onset of

bacteremia, but raised levels are not specific for bacterial infection.[7] Recently many investigators have considered CRP estimation to be of value in early diagnosis and monitoring of neonatal sepsis. However, in a large study from New York CRP value was found to be moderately raised in sepsis but the serum level were also found high with asphyxia, shock and other problems not related to infection.[8, 9] The frequent occurrence of raised CRP in sera of uninfected newborn infants eliminates it as a useful indicator of infection but may suggest an active tissue damaging process.[10] In our study CRP was found positive is 52 percent of culture negative cases while it was negative in 33 percent of culture proven sepsis. Thus the question, with a positive test that how likely is the disease not to be present remains to be answered.

We used latex agglutination slide test for CRP, which is simple to perform and easy to interpret but CRP can also be detected by quantitative radioimmunodiffusion technique. It should be emphasized that qualitative test is nonspecific and must be correlated with other laboratory data and clinical finding while on the other hand quantitative technique is comparatively less non specific but process requires more time which may be too long a period to deal with an acutely ill neonate.

Furthermore, these test can become positive in variety of non- infective disorders, septicemia can occur with normal findings, therefore we do not advocate to rely on the result of single test, even with the clinical and laboratory data. CRP can not be relied upon as a good screening test for infection on its own but can be made part of a scoring system, along with complete blood count and clinical criteria, in order to avoid delay in initiation of antibiotic therapy for infected neonates while avoiding their indiscriminate use for all sick neonates

CONCLUSIONS

This is an initial workup study and we recommend that a scoring system should be designed for our setup. It should be based on those tests that are easy to perform, economical, available should have high predictive value and should ideally identify all infected infants (high sensitivity). This will ensure that disease can be confidently excluded with negative test result (high negative predictive value), and antibiotic therapy is stopped early. It will reduce the cost, duration of hospital stay and anxiety of the parents besides avoiding delay in initiation of antibiotic therapy for infected neonates.

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